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RESEARCH PAPER

Safety and immunogenicity of 15-valent pneumococcal conjugate vaccine (PCV-15) compared to PCV-13 in healthy older adults

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ABSTRACT

Background: Pneumococcal disease remains a public health priority in adults. Safety and immunogenicity of 2 different formulations of 15-valent pneumococcal conjugate vaccine (PCV15) containing 13 serotypes included in 13-valent pneumococcal conjugate vaccine (PCV13) plus 2 additional serotypes (22F and 33F) were evaluated in adults ≥ 50 years (V114-006; NCT02547649).
Methods: A total of 690 subjects (230/arm) received a single dose of either PCV15 Formulation A, PCV15 Formulation B, or PCV13 and were followed for safety for 14 days postvaccination. Serotype-specific opsonophagocytic activity (OPA) geometric mean titers (GMTs) and Immunoglobulin G (IgG) geometric mean concentrations (GMCs) were measured immediately prior and 30 days postvaccination.
Results: Both PCV15 formulations had generally comparable safety profiles to PCV13. Baseline IgG GMCs and OPA GMTs were comparable across vaccination groups. At 30 days postvaccination, both PCV15 formulations induced serotype specific antibodies to all 15 serotypes in the vaccine. IgG GMCs and OPA GMTs in recipients of either PCV15 formulation were non-inferior (≤ 2-fold margin) to those measured in recipients of PCV13 for shared serotypes and superior (> 1.0-fold difference) for serotypes unique to PCV15. Formulation B generally induced higher immune responses than Formulation A.
Conclusion: In healthy adults ≥ 50 years of age, both new formulations of PCV15 displayed acceptable safety profiles and induced serotype-specific immune responses comparable to PCV13.

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Introduction

Pneumococcal disease (PD) is associated with significant morbidity and mortality worldwide. Children < 5 years of age, older adults ≥ 65 years of age, and individuals of any age with certain medical conditions (i.e., cancer, chronic heart disease, chronic lung disease, and diabetes mellitus) are at increased risk for pneumococcal disease.[1,2] High incidence of disease in older adults is due to immune senescence and physiological changes in the respiratory system associated with aging.[3] Invasive pneumococcal disease (IPD) includes disease with high degree of invasiveness such as meningitis, bacteremia/sepsis, and bacteremic pneumonia. Non-invasive disease includes sinusitis, otitis media, and non-bacteremic pneumonia.[4] Incidence of pneumococcal pneumonia without bacteremia is difficult to estimate due to limited use in clinical practice of confirmatory laboratory test despite recent development of new urinary tests aimed at detecting all or serotype-specific cases of non-bacteremic pneumococcal pneumonia.[5–7]

Several pneumococcal polysaccharide vaccines (PPVs) containing capsular polysaccharides from 6 to 23 serotypes have been developed since the 1970s. Currently, only the 23-valent pneumococcal polysaccharide vaccine (PPV23) is licensed in many countries worldwide. Effectiveness of PPV23 against IPD in immunocompetent adults has generally ranged from 56-to-81%, but is lower in immunocompromised individuals.[8] Additionally, the vaccine was found to be ineffective in children < 2 years of age due to the immaturity of their immune system. Efficacy of PPV23 against pneumococcal pneumonia was demonstrated in several studies but rates varied between studies.[9–14] Although underused, PPVs were shown to be efficacious and cost-effective against pneumococcal disease.[15–17]

In order to improve vaccine effectiveness in children, several pneumococcal conjugate vaccines (PCV7 [Prevnar™, Pfizer, Philadelphia], PCV10 [Synflorix™, GlaxoSmithKline, Rixensart, Belgium], and PCV13 [Prevnar 13™, Pfizer, Philadelphia, PA]) have been licensed since 2000. Efficacy of PCV7 against IPD was demonstrated in several pediatric clinical trials[18–20] and effectiveness of both PCV10 and PCV13 against IPD and otitis media has been observed in children < 5 years of age.[21–24] Recently, a placebo-controlled study (CAPiTA) showed PCV13 to be 45.6% efficacious in preventing first episode of vaccine-type (VT) pneumococcal

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Supplemental data can be accessed here.

pneumonia and 75% against VT-IPD but did not improve overall survival of vaccinated adults ≥ 65 years of age compared to placebo.[7] Based on CAPiTA results, sequential dosing regimen of PCV13 followed by PPV23 administered 1 year later was adopted in the U.S. for adults ≥ 65 years of age but usage of PCV13 in adults remains undecided in most countries with established childhood PCV programs.

Widespread use of these vaccines has led to significant reduction in nasopharyngeal carriage, IPD, and pneumococcal pneumonia in the population targeted by vaccination but also in other age groups (herd protection). For all age groups, greater impact has been observed in disease caused by vaccine serotypes whereas cases of IPD caused by non-vaccine serotypes have increased over time.[25–31] Interestingly, disease caused by serotypes not included in newly licensed vaccines, including 22F and 33F, also increased in recent years.[32–34] Vaccine impact was observed for both IPD and pneumococcal pneumonia.[32–38]

A 15-valent pneumococcal conjugate vaccine (PCV15) comprised of serotypes 1, 3, 4, 5, 6A, 6B, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, and 33F has the potential to address important medical and public health needs by providing broader coverage for leading serotypes associated with pneumococcal disease worldwide.[39] In comparison to PCV13, the 2 serotypes unique to PCV15 (22F and 33F) are among leading serotypes causing IPD in children and adults following widespread use of PCV13 in children in many countries, likely due to their invasiveness capacity.[25,28,32–34] By 2013 in the US, residual IPD caused by serotype 22F among children < 5 years and adults ≥ 18 years were 11% and 13%, respectively while serotype 33F caused 10% and 5% of residual IPD cases in children < 5 years and adults ≥ 18 years, respectively.[33] The current study (V114-006; NCT02547649) compared safety and immunogenicity of a single dose of 2 different formulations of PCV15 to PCV13 in pneumococcal vaccine-naïve adults ≥ 50 years of age. Both PCV15 formulations (PCV15-A and PCV15-B) contain 15 pneumococcal polysaccharides conjugated to a carrier protein (diphtheria CRM_{197} protein) and are formulated with aluminum phosphate adjuvant. PCV15-A utilizes the same conjugation process for all 15 glycoconjugates. PCV15-B utilizes the same conjugation as PCV15-A for 8 serotypes and a modified process for 7 serotypes. These modifications were aimed at improving overall stability of the investigational vaccine over its shelf-life as well as immune recognition of glycoconjugates in both adults and children.

Results

Study subjects

Of 689 vaccinated subjects, nearly all (98.4%) completed all study-required procedures and study visits (Figure 1). Across the 3 vaccination groups, subjects were equally distributed with respect to age, gender, race/ethnicity, presence of key pre-existing medical conditions [i.e., chronic heart disease, chronic obstructive pulmonary disease (COPD), and diabetes mellitus], as well as prior and concomitant therapies (Supplemental Table 1). In each vaccination group, subjects were equally distributed into protocol-specified age cohorts (50–64 years, 65–74 years, and ≥ 75 years) and approximately 50% of subjects were ≥ 65 year of age.

Safety

Majority of subjects reported at least one injection-site or systemic adverse event (AE). Most of these AEs were those solicited in the vaccination report card (VRC) and included conditions commonly observed in older adults. Serious AEs (SAEs) were rarely reported and none was related to study

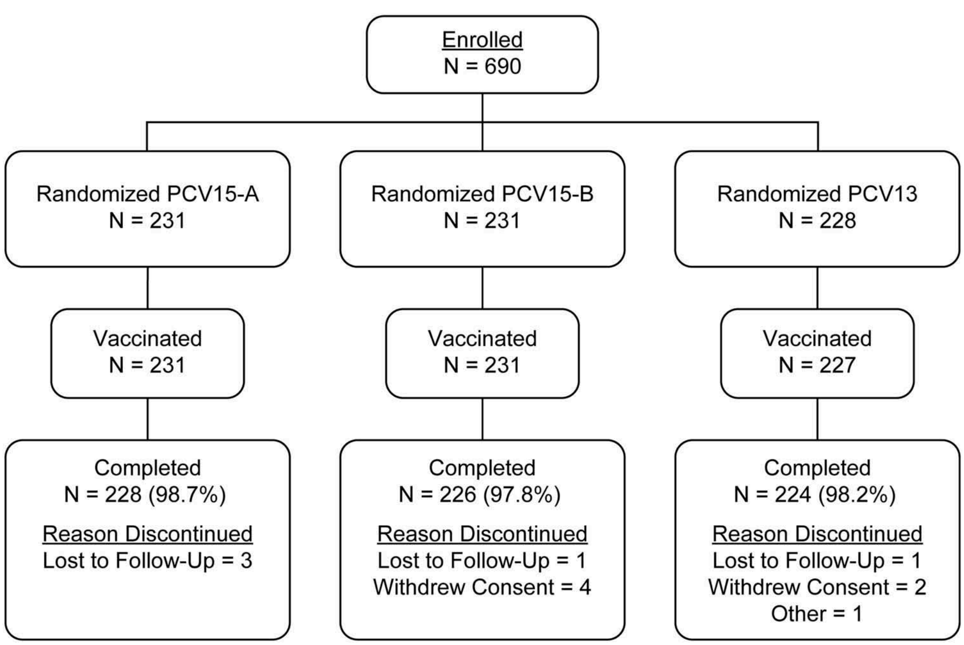

Figure 1. Subject disposition.

Table 1. Subjects reporting local and systemic adverse events within 14 days postvaccination.

	PCV15 – A		PCV15-B		PCV13	
	n	(%)	n	(%)	n	(%)
Subjects With Safety Follow-up	**231**		**231**		**227**	
Injection-site AEs (Day 1 to Day 14 Following Vaccination)	153	(66.2)**	152	(65.8)	130	(57.3)
Injection-site pain	145	(62.8)	140	(60.6)	124	(54.6)
Injection-site erythema	22	(9.5)	29	(12.6)	24	(10.6)
Injection-site swelling	29	(12.6)	38	(16.5)	29	(12.8)
Systemic AEs (Day 1 to Day 14 Following Vaccination)	109	(47.2)	94	(40.7)	93	(41.0)
Fatigue	56	(24.2)	41	(17.7)	51	(22.5)
Arthralgia	22	(9.5)	17	(7.4)	14	(6.2)
Myalgia	53	(22.9)**	43	(18.6)	32	(14.1)
Headache	28	(12.1)	29	(12.6)	38	(16.7)
Serious AEs (Duration of the Study)						
with serious adverse events	1	(0.4)	2	(0.9)	0	(0.0)
with vaccine-related† serious adverse events	0	(0.0)	0	(0.0)	0	(0.0)
who died	0	(0.0)	0	(0.0)	0	(0.0)
who discontinued due to adverse event	0	(0.0)	0	(0.0)	0	(0.0)
Elevated Body Temperature (Day 1 to Day 5 Following Vaccination)	225		224		223	
< 100.4 °F (38.0 °C)	223	(99.1)	221	(98.7)	223	(100)
≥ 100.4 °F (38.0 °C) and < 102.2 °F (39.0 °C)	2	(0.9)	2	(0.9)	0	(0.0)
≥ 102.2 (39.0 °C) and < 103.1°F (39.5 °C)	0	(0.0)	1	(0.4)	0	(0.0)
≥ 103.1°F (39.5 °C)	0	(0.0)	0	(0.0)	0	(0.0)

† Determined by the investigator to be related to the vaccine
** Statistically higher when compared with PCV13 (unadjusted p-value < 0.05).

vaccine. During the study period, no death was reported and no subject was discontinued due to an AE. Most commonly reported AEs were injection site pain/tenderness, swelling, and erythema, as well as systemic events of fatigue, myalgia, headache, and arthralgia (Table 1). Reporting rates of solicited events were generally comparable across vaccination groups and most events were transient (lasting 1-to-3 days), and mild-to-moderate in intensity. Rates of injection site AEs were higher in recipients of PCV15-A and PCV15-B than recipients of PCV13 and the observed differences were mainly due to higher frequencies of injection site pain/tenderness. No specific trends were observed when comparing reporting rates of other injection site AEs (swelling and erythema) or systemic AEs across vaccination groups. Although the reporting rates of overall injection site AEs and myalgia were statistically higher in recipients of PCV15-A than PCV13 (p-value < 0.05), these differences were not clinically significant (most of these AEs were transient, mild-to-moderate in intensity) and could be due to chance given the many AE comparisons analyzed. Elevated body temperature was rarely reported and no study subject reported body temperature ≥ 39.5°C (oral) during the 5 days postvaccination (Table 1).

Immunogenicity

At 1-month postvaccination, both PCV15-A and PCV15-B were non-inferior to PCV13 for all 13 shared serotypes, as lower bounds of 95% CIs for OPA GMT ratios (PCV15-A/PCV13 and PCV15-B/PCV13) were all > 0.33 (Figure 2). Although not hypothesized in this trial, either formulations of PCV15 were also non-inferior to PCV13 if a more stringent criterion of 2-fold difference in OPA GMTs (lower bound of 95% confidence interval of serotype-specific OPA GMT ratios being ≥ 0.5) was tested. Both PCV15-A and PCV15-B were superior to PCV13 for the 2 serotypes unique to PCV15 (22F and 33F) as the lower bounds of two-sided 95% CI of GMT ratios (PCV15-A/PCV13 and PCV15-B/PCV13) were > 1.0. Comparisons of serotype-specific IgG GMC ratios based on 2-fold difference between recipients of either PCV15-A or PCV15-B and PCV13 mimicked those observed using OPA GMTs and confirmed that both formulations of PCV15 were non-inferior to PCV13 (Figure 3). Although no formal comparison was performed between PCV15-A and PCV15-B, recipients of PCV15-B tended to have higher levels of OPA GMTs and IgG GMCs for serotypes manufactured with the modified conjugation process; however, improvement for these serotypes was associated with some reduction, albeit minimal, on antibody titers to serotypes using the same conjugation process in both formulations A and B (e.g., serotypes 9V and 14) (Figures 2,3). As geometric mean antibody concentrations or titers do not fully describe the overall performance of a given vaccine and potential differences across a range of antibody titers, we also analyzed reverse cumulative distribution curves (RCDCs) of serotype-specific IgG GMCs and opsonophagocytic killing activity (OPA) GMTs between recipients of PCV15-A, PCV15-B, and PCV13. RCDCs showed comparable performance of the 3 study vaccines for most shared serotypes and higher levels of serotype-specific OPA GMTs and IgG GMCs for serotypes 22F and 33F among recipients of either PCV15-A or PCV15-B than PCV13 (Supplementary Figures 1 and 2).

Baseline serotype-specific IgG GMCs and OPA GMTs were comparable across vaccination groups and significant increases were observed at 30 days postvaccination to all serotypes included in study vaccines. For shared serotypes between study vaccines, geometric mean fold-rises (GMFRs) and OPA GMTs varied by serotype and were generally comparable across the vaccination groups. OPA GMFR was lowest for serotype 3 and highest for serotype 6A or serotype 6B for all 3 vaccination groups, ranging from 11.26 (serotype 3) to 85.26 (serotype 6B) among recipients of PCV15-A, from 6.93

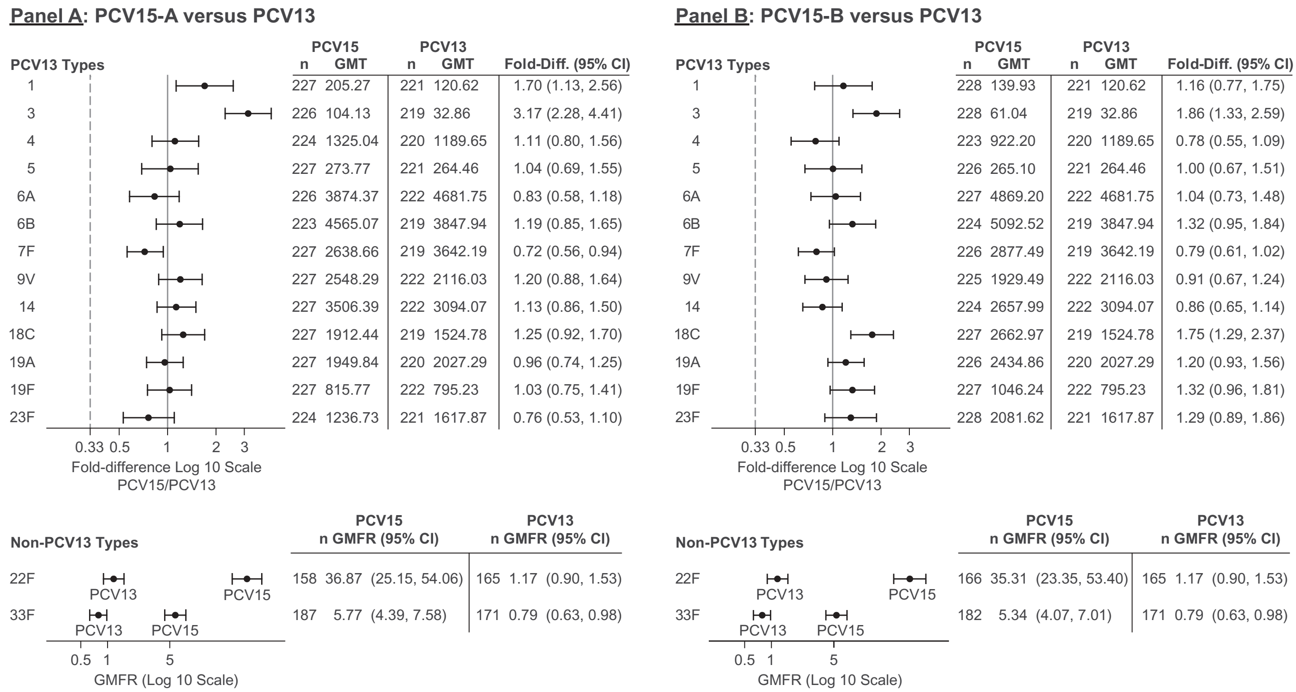

Figure 2. PCV15-A and PCV15-B versus PCV13 OPA GMT ratios at 1 month postvaccination.

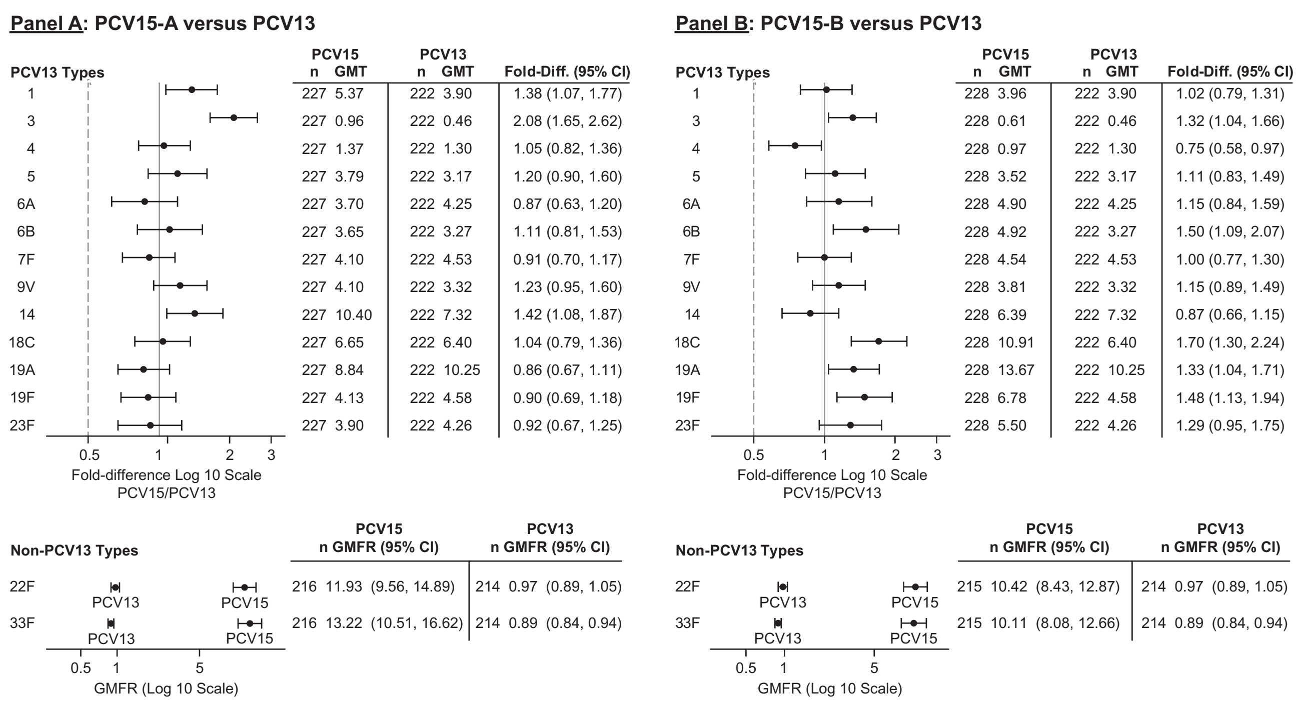

Figure 3. PCV15-A and PCV15-B versus PCV13 IgG GMC ratios at 1 month postvaccination.

(serotype 3) to 123.84 (serotype 6A) among recipients of PCV15-B, and from 4.26 (serotype 3) to 77.52 (serotype 6A) among recipients of PCV13 (Table 2). IgG GMFRs for the shared serotypes varied by serotype and vaccination groups, ranging from 6.00 (serotype 3) to 15.34 (serotype 1) among recipients of PCV15-A, from 4.00 (serotype 3) to 20.68 (serotype 18C) among recipients of PCV15-B, and from 3.08 (serotype 3) to 15.14 (serotype 6A) among recipients of PCV13 (Table 3).

Both serotypes 22F and 33F are included in PCV15 but not in PCV13. OPA GMFRs for serotypes 22F and 33F were 36.87 and 5.77, respectively for recipients of PCV15-A and 35.31 and 5.34, respectively for recipients of PCV15-B. As expected, no increase was observed for these serotypes following vaccination with

Table 2. Summary of OPA antibody responses – geometric mean fold rise (GMFR) (per protocol population).

Pneumococcal Serotype	Endpoint	PCV15-A (N = 231) n	PCV15-A Observed Response	PCV15-A 95% CI	PCV15-B (N = 231) n	PCV15-B Observed Response	PCV15-B 95% CI	PCV13 (N = 227) n	PCV13 Observed Response	PCV13 95% CI
1	GMFR	203	17.51	(13.24, 23.15)	199	12.44	(9.44, 16.38)	201	10.23	(7.75, 13.51)
3		202	11.26	(9.04, 14.01)	201	6.93	(5.65, 8.52)	195	4.26	(3.41, 5.33)
4		191	63.05	(46.61, 85.28)	180	34.45	(24.49, 48.46)	185	53.97	(37.91, 76.83)
5		195	17.47	(12.97, 23.55)	194	17.22	(12.76, 23.25)	198	16.54	(12.28, 22.28)
6A		201	79.98	(56.75, 112.72)	199	123.84	(85.02, 180.38)	199	77.52	(52.77, 113.89)
6B		185	85.26	(62.13, 117.02)	181	93.44	(65.95, 132.40)	183	65.08	(45.88, 92.32)
7F		187	12.73	(9.90, 16.37)	191	17.95	(13.77, 23.39)	188	20.94	(15.75, 27.84)
9V		195	15.92	(11.35, 22.32)	188	10.29	(7.54, 14.04)	190	13.00	(9.35, 18.07)
14		198	10.05	(7.33, 13.80)	197	7.30	(5.36, 9.93)	205	8.73	(6.20, 12.29)
18C		191	27.42	(19.50, 38.56)	185	29.19	(20.23, 42.10)	185	19.26	(13.30, 27.91)
19A		187	27.56	(19.94, 38.09)	196	24.06	(17.49, 33.09)	197	23.52	(17.00, 32.53)
19F		198	22.29	(16.64, 29.86)	201	23.89	(17.59, 32.45)	200	20.65	(15.18, 28.09)
23F		194	24.11	(18.05, 32.20)	185	35.40	(25.77, 48.64)	190	34.22	(24.82, 47.18)
22F		158	36.87	(25.15, 54.06)	166	35.31	(23.35, 53.40)	165	1.17	(0.90, 1.53)
33F		187	5.77	(4.39, 7.58)	182	5.34	(4.07, 7.01)	171	0.79	(0.63, 0.98)

N = Number of subjects randomized and vaccinated.
n = Number of subjects contributing to the analysis.
CI = Confidence interval.
GMT = Geometric mean titer (1/dil).
GMFR = Geometric mean fold-rise from Day 1.

Table 3. Summary of IgG antibody responses – GMFR (per protocol population).

Pneumococcal Serotype	Endpoint	PCV15-A (N = 231) n	PCV15-A Observed Response	PCV15-A 95% CI	PCV15-B (N = 231) n	PCV15-B Observed Response	PCV15-B 95% CI	PCV13 (N = 227) n	PCV13 Observed Response	PCV13 95% CI
1	GMFR	216	15.34	(12.30, 19.13)	215	10.62	(8.68, 13.00)	214	9.72	(7.89, 11.99)
3		216	6.00	(5.02, 7.17)	215	4.00	(3.44, 4.66)	214	3.08	(2.62, 3.61)
4		216	9.17	(7.50, 11.21)	215	6.82	(5.69, 8.16)	214	8.35	(6.81, 10.23)
5		216	6.03	(4.89, 7.44)	215	5.73	(4.66, 7.05)	214	5.07	(4.13, 6.24)
6A		216	13.44	(10.83, 16.68)	215	17.60	(14.01, 22.12)	214	15.14	(11.90, 19.27)
6B		216	12.55	(10.19, 15.46)	215	17.94	(14.19, 22.67)	214	11.88	(9.30, 15.17)
7F		216	9.76	(7.98, 11.94)	215	11.18	(9.12, 13.71)	214	10.75	(8.73, 13.24)
9V		216	11.57	(9.44, 14.18)	215	11.35	(9.21, 13.98)	214	9.53	(7.79, 11.65)
14		216	7.88	(6.21, 9.99)	215	4.87	(3.98, 5.96)	214	5.62	(4.49, 7.04)
18C		216	13.43	(10.73, 16.82)	215	20.68	(16.12, 26.54)	214	12.42	(9.91, 15.57)
19A		216	8.28	(6.84, 10.02)	215	10.80	(8.77, 13.30)	214	8.69	(7.13, 10.58)
19F		216	7.46	(6.09, 9.15)	215	11.57	(9.30, 14.41)	214	7.85	(6.46, 9.55)
23F		216	11.31	(9.07, 14.09)	215	15.70	(12.46, 19.78)	214	12.71	(10.07, 16.04)
22F		216	11.93	(9.56, 14.89)	215	10.42	(8.43, 12.87)	214	0.97	(0.89, 1.05)
33F		216	13.22	(10.51, 16.62)	215	10.11	(8.08, 12.66)	214	0.89	(0.84, 0.94)

N = Number of subjects randomized and vaccinated.
n = Number of subjects contributing to the analysis.
CI = Confidence interval.
GMC = Geometric mean concentration (μg/mL).
GMFR = Geometric mean fold-rise from Day 1.

PCV13 (Table 2). Similar trends were observed for IgG GMFRs for serotypes 22F and 33F across vaccination groups (Table 3).

Responses to vaccination were also analyzed by computing the proportion of study subjects achieving ≥ 4-fold increase in OPA GMTs and IgG GMCs from prevaccination to 30 days postvaccination. Overall, proportions of subjects with such increase in OPA response were comparable across vaccination groups for any given shared serotype, ranging from 61.6% (serotype 14) to 87.0% (serotype 6B) among recipients of PCV15-A, from 50.3% (serotype 14) to 87.3% (serotype 6B) among recipients of PCV15-B, from 44.1% (serotype 3) to 84.2% (serotype 6B) among recipients of PCV13 (Table 4). As expected, more recipients of either PCV15-A or PCV15-B than PCV13 achieved 4-fold increase in OPA GMTs from baseline to postvaccination for 22F and 33F (Table 4). The analyses of the proportion of subjects achieving 4-fold increase in serotype-specific IgG GMCs from baseline to postvaccination followed the same trends as OPA responses.

We performed a subgroup analysis of vaccine-induced immune responses (OPA GMTs and IgG GMCs) by age stratum (50-to-64 years, 65-to-74 years, and ≥ 75 years). Responses varied by serotype but were comparable across the 3 vaccination groups. For the majority of shared serotypes, older subjects ≥ 75 years of age tended to have numerically lower OPA GMTs and IgG GMCs than those in younger age groups although antibody levels for a given serotype did overlap across the 3 age strata (Figure 4A,B). Furthermore and within each vaccination group, levels of vaccine-induced antibodies varied between subjects with underlying chronic heart disease, chronic lung disease, diabetes mellitus or those not reporting any of these conditions; however, no differences were observed when comparing IgG GMCs and OPA GMTs

Table 4. Summary of OPA antibody responses – %≥ 4 fold rise (per protocol population).

		PCV15-A (N = 231)			PCV15-B (N = 231)			PCV13 (N = 227)		
Pneumococcal			Observed			Observed			Observed	
Serotype	Endpoint	n	Response	95% CI	n	Response	95% CI	n	Response	95% CI
1	%≥ 4 fold rise	203	70.9% (144/203)	(64.17, 77.08)	199	66.3% (132/199)	(59.31, 72.86)	201	61.7% (124/201)	(54.59, 68.44)
3		202	71.8% (145/202)	(65.04, 77.87)	201	64.2% (129/201)	(57.13, 70.80)	195	44.1% (86/195)	(37.01, 51.37)
4		191	84.8% (162/191)	(78.93, 89.59)	180	78.9% (142/180)	(72.19, 84.61)	185	81.6% (151/185)	(75.28, 86.92)
5		195	68.2% (133/195)	(61.17, 74.67)	194	70.6% (137/194)	(63.67, 76.93)	198	67.2% (133/198)	(60.16, 73.66)
6A		201	85.1% (171/201)	(79.38, 89.70)	199	82.9% (165/199)	(76.95, 87.87)	199	82.9% (165/199)	(76.95, 87.87)
6B		185	87.0% (161/185)	(81.31, 91.51)	181	87.3% (158/181)	(81.55, 91.77)	183	84.2% (154/183)	(78.04, 89.12)
7F		187	67.9% (127/187)	(60.71, 74.54)	191	74.3% (142/191)	(67.54, 80.38)	188	75.0% (141/188)	(68.18, 81.02)
9V		195	64.6% (126/195)	(57.46, 71.31)	188	59.6% (112/188)	(52.19, 66.65)	190	60.5% (115/190)	(53.19, 67.53)
14		198	61.6% (122/198)	(54.46, 68.42)	197	50.3% (99/197)	(43.06, 57.44)	205	48.3% (99/205)	(41.28, 55.36)
18C		191	74.9% (143/191)	(68.10, 80.85)	185	73.0% (135/185)	(65.97, 79.23)	185	64.3% (119/185)	(56.96, 71.22)
19A		187	74.9% (140/187)	(68.02, 80.91)	196	73.0% (143/196)	(66.17, 79.04)	197	71.1% (140/197)	(64.19, 77.29)
19F		198	74.2% (147/198)	(67.56, 80.18)	201	72.1% (145/201)	(65.40, 78.22)	200	75.5% (151/200)	(68.94, 81.29)
23F		194	76.3% (148/194)	(69.67, 82.09)	185	81.1% (150/185)	(74.68, 86.45)	190	78.9% (150/190)	(72.46, 84.51)
22F		158	76.6% (121/158)	(69.20, 82.94)	166	71.1% (118/166)	(63.55, 77.85)	165	14.5% (24/165)	(9.55, 20.87)
33F		187	53.5% (100/187)	(46.05, 60.79)	182	58.8% (107/182)	(51.27, 66.02)	171	8.8% (15/171)	(4.99, 14.06)

N = Number of subjects randomized and vaccinated.
n = Number of subjects contributing to the analysis.
CI = Confidence interval.
GMT = Geometric mean titer (1/dil).
GMFR = Geometric mean fold-rise from Day 1.

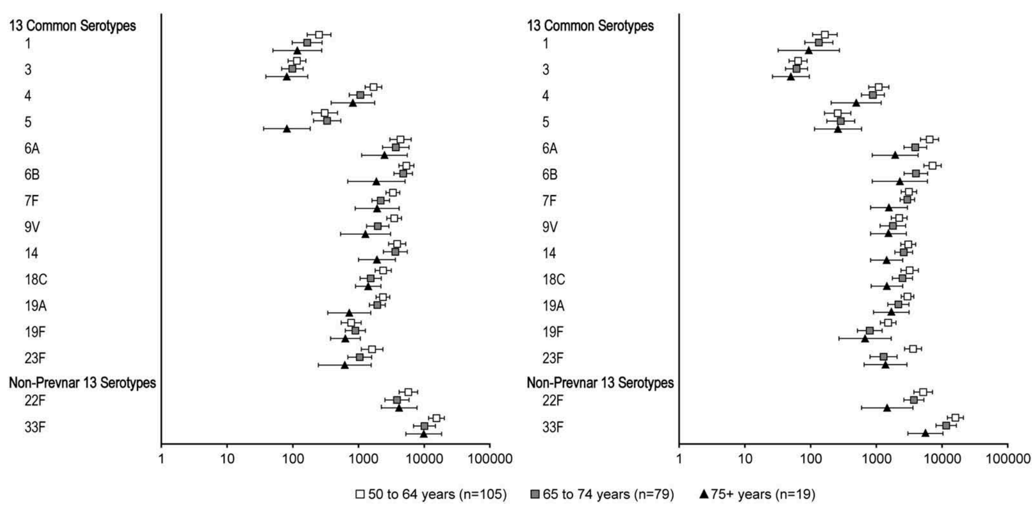

Figure 4. Serotype-specific OPA GMTs by age stratum [PCV15-A (left); PCV15-B (right)]

among subjects with or without history of either chronic condition who received the same study vaccine (Supplementary Tables 2 and 3).

Discussion

The significant reduction in the burden of pneumococcal disease in both children and adults worldwide over the last 2 decades underscores the public health value of infant immunization with PCVs. Widespread use of PCVs in children has significantly decreased nasopharyngeal colonization and IPD by serotypes included in the vaccine in other age groups not targeted by the vaccination program.[25] Notwithstanding, nonbacteremic pneumonia remains an important unmet medical need in older adults. It is therefore conceivable that direct immunization of older adults with PCVs could further reduce burden of nonbacteremic pneumococcal pneumonia.[7]

Our study compared the tolerability, safety, and immunogenicity profiles of 2 new formulations of PCV15 in adults ≥ 50 years of age. Although these new PCV15 formulations differ in the processes used to manufacture glycoconjugates for some serotypes, the nature of the key vaccine ingredients are generally similar and comparable to an earlier formulation evaluated in children and adults.[40,41] Study results showed that both PCV15-A and PCV15-B displayed tolerability and safety profiles comparable to PCV13 with regard to the nature, frequency, duration, and severity of AEs over the protocol-specified safety follow-up period. With the exception of higher rates of injection site pain/tenderness observed in recipients of both PCV15-A and PCV15-B than in PCV13, no specific trends were observed when comparing reporting rates of other injection-site or systemic AEs across vaccination groups.

Overall, baseline and postvaccination serotype-specific IgG GMCs and OPA GMTs, GMFRs as well as proportions of subjects with ≥ 4-fold increase in antibody titers from baseline varied by serotype but were generally comparable for each shared serotype across vaccination groups. Both PCV15-A and PCV15-B were non-inferior to PCV13 for all 13 shared serotypes, and superior to PCV13 for the 2 serotypes (22F and 33F) unique to PCV15. Of interest, both PCV15 formulations elicited higher OPA GMTs and IgG GMCs than PCV13 to serotype 3, a serotype that is still associated with a significant burden of pneumococcal disease in children and older adults despite high uptake of PCV13 in children in many countries for several years.[42–44] Although serotype-specific OPA GMTs or IgG GMCs were observed to be numerically higher for a given study vaccine than the 2 other study vaccines, the clinical significance of such differences are unknown as no serotype-specific correlate of protection against pneumococcal disease has been established in adults. No clear underlying biological or chemical reasons were found and such differences could be due to chance alone given the number of comparisons tested between PCV15-A, PCV15-B and PCV13. Although the study was not aimed at comparing the immune responses between PCV15-A and PCV15-B, recipients of PCV15-B tended to have higher levels of OPA GMTs and IgG GMCs for most serotypes included in PCV15.

Our study has several limitations. Study population only included subjects with stable underlying medical conditions and vaccine performance in those with immunocompromising conditions was therefore not demonstrated. The lack of immune correlates of protection against pneumococcal disease in adults did not allow for use of a clinically relevant biomarker to assess potential efficacy of PCV15. The study was not powered to evaluate the impact of either study vaccine on pneumococcal disease. As we only measured immune responses at baseline and 30 days postvaccination, no information can be provided about long-term persistence of vaccine-induced immune responses in recipients of either formulation of PCV15. Furthermore, our study was not powered to statistically compare the safety and immunogenicity profiles between PCV15-A and PCV15-B. Finally and given the small number of subjects with each of the medical comorbid conditions or within each age stratum among recipients of either PCV15 formulation or PCV13, no statistical analysis was performed to compare the impact of age or comorbid condition on the safety and immunogenicity of PCV15-A or PCV15-B and PCV13, nor the impact of age or comorbid condition on the safety and immunogenicity within each vaccination group.

Overall, both formulations of PCV15 are highly immunogenic and induce both OPA and IgG antibodies to all 15 serotypes included in the vaccine at levels comparable to PCV13 for shared serotypes. An important benefit afforded by PCV15 in comparison to PCV13 is the induction of high levels of antibodies to serotypes 22F and 33F which have emerged as leading causes of IPD in both children and older adults following widespread use of PCVs in many countries worldwide. Although both PCV15 formulations elicited higher OPA GMT and IgG GMC to serotype 3 than PCV13, it remains to be seen whether such trends in antibody responses could translate into greater effectiveness against disease caused by serotype 3. Taken together, the demonstrated acceptable safety and immunogenicity profiles of PCV15 in our study supports further development of PCV15. If licensed, PCV15 will increase availability of more PCVs and help in the worldwide effort to end preventable child and adult deaths from pneumococcal disease.

Methods

Participants and study design

This phase 2 randomized, double-blind trial was conducted at 23 clinical sites in the United States to compare the safety, tolerability and immunogenicity of a single dose of 2 different formulations of PCV15 (PCV15-A and PCV15-B) to PCV13 in pneumococcal vaccine-naïve adults ≥ 50 years of age. Key eligibility criteria were no previous pneumococcal vaccination, stable underlying medical condition, and absence of protocol-defined known or suspected immunocompromising conditions (e.g., HIV infection, generalized malignancy). The protocol was approved by ethical review committees of each site and conducted in conformance with applicable country or local requirements. Written informed consent was obtained from each subject prior to the performance of any study procedure.

A total of 689 community-dwelling adults were randomly given a single dose of PCV15-A, PCV15-B, or PCV13. All subjects were followed for AEs for 14 days postvaccination. Solicited injection-site AEs included redness, swelling, and pain/tenderness; and solicited systemic AEs included muscle pain (myalgia), joint pain (arthralgia), headache, and fatigue. SAEs were collected through 30 days postvaccination and/or completion of subject's participation in study. Daily oral temperature was collected for first 5 days postvaccination.

Blood samples were collected prior and 30 days postvaccination and sera were used to measure serotype-specific OPA and Immunoglobulin G (IgG) antibodies to all 15 vaccine serotypes included in PCV15. Functional opsonophagocytic activity was measured using multiplex OPA (MOPA) assay (Prof. David Goldblatt, Institute of Child Health, London, UK)[45]. Serotype-specific IgG was measured using pneumococcal electrochemiluminescence (ECL) assay (Meso Scale Diagnostics, Gaithersburg, MD) at PPD Laboratories' bioanalytical lab (Richmond, VA)[46].

Vaccines

Each dose of PCV15 contains 2µg of pneumococcal capsular polysaccharide from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 22F, 23F, 33F and 4µg of serotype 6B conjugated with 32µg of CRM_{197} and formulated with 125µg of aluminum phosphate adjuvant per 0.5mL dose. PCV15-A used the same conjugation process for all 15 serotypes. In PCV15-B, a modified conjugation process was implemented for 7 out of the 15 serotypes (6A, 6B, 7F, 18C, 19A, 19F, and 23F). Both PCV15 formulations contain a surfactant: Poloxamer 188 in

PCV15-A and Polysorbate 20 in PCV15-B. PCV13 contains 2.2µg of polysaccharides from serotypes 1, 3, 4, 5, 6A, 7F, 9V, 14, 18C, 19A, 19F, 23F and 4.4µg of serotype 6B conjugated to 34µg of CRM_{197} and formulated with 125µg of aluminum phosphate adjuvant.

Statistical methods

Proportions of subjects reporting AE following vaccination were compared between PCV15 groups and PCV13. Study primary immunogenicity objective was to demonstrate that PCV15-A or PCV15-B were non-inferior to PCV13 for 13 shared serotypes and superior to PCV13 for the 2 non-shared serotypes (22F and 33F) at 1-month postvaccination. Non-inferiority was declared if lower bound of two-sided 95% CI of the OPA GMT ratios (PCV15/PCV13) for each shared serotype was > 0.33 (3-fold non-inferiority margin). Superiority was declared if lower bound of the two-sided 95% CI of the OPA GMT ratio (PCV15/PCV13) was > 1.0 for both 22F and 33F. A secondary non-inferiority immunogenicity hypothesis assessed PCV15 and PCV13 with respect to IgG GMCs for 13 shared serotypes and superiority for 2 unique serotypes. Non-inferiority was declared if lower bound of two-sided 95% CI of IgG GMC ratios (PCV15/PCV13) for each shared serotype was > 0.5 (2-fold non-inferiority margin). Superiority was declared if lower bound of the two-sided 95% CI of the GMC ratio (PCV15/PCV13) was > 1.0 for both 22F and 33F. GMC/GMT ratio estimation, 95% CI, and hypothesis test (1-sided p-value) were calculated using constrained longitudinal data analysis method[47]. Additional secondary objectives included summaries of geometric mean fold-rises, proportion of subjects with ≥ 4-fold rise from baseline in recipients of PCV15-A, PCV15-B, and PCV13 for all 15 serotypes contained in PCV15. The sample size was determined through simulations based on results from prior Phase 2 studies under the assumption that the natural logarithm of the Day 1 and Day 30 OPA responses follow a bivariate normal distribution for each serotype. A sample size of ~ 230 adults per vaccination group provided at least 90% power to demonstrate non-inferiority and superiority for at least one of the PCV15 formulations based on OPA. The success of either PCV15-A or PCV15-B required success on both non-inferiority to PCV13 for the 13 shared serotypes and superiority to PCV13 for the 2 unique serotypes.

Disclosure of potential conflicts of interest

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Author Contributions

HL Stacey, J Rosen, and JT Peterson: enrollment of subjects and/or data collection, review of the manuscript.

V Gakhar, TM Sterling, CJ Acosta, K Nolan, J Li, P Benner, C Abeygunawardana, M Mosinski, WJ Smith, and H Pujar: analysis and interpretation of data, and preparation of manuscript.

A Williams-Diaz, A Pedley, and LK Musey: study concept and design, analysis and interpretation of data, and preparation of manuscript.

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